# BRACAnalysis CDx™, Tumor BRACAnalysis CDx™, myChoice HRD™ - *A portfolio of Companion Diagnostic Products to optimize therapeutic selection for cancer patients*

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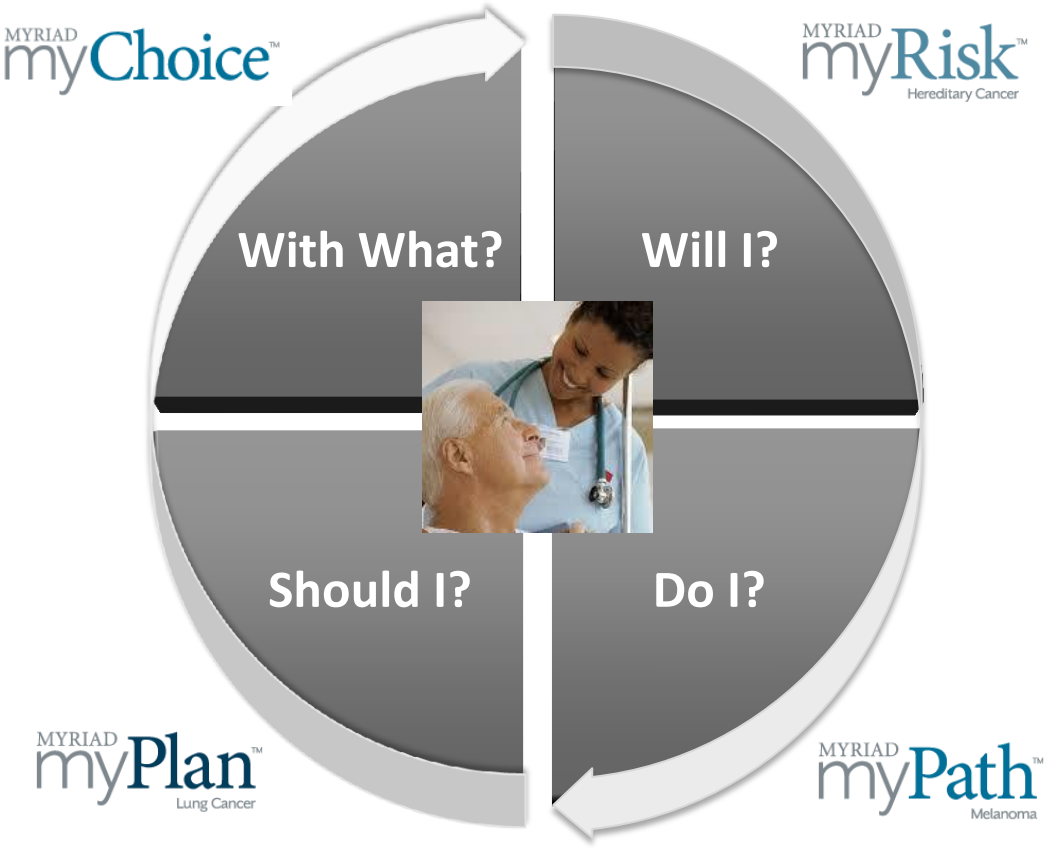
**NMBio**
**Aug 11**

# Agenda

- Introduction (this slide)
- A Myriad CDx Story
  - Brief story of 3 Myriad CDx products: BRACAnalysis CDx, tumor BRACAnalysis CDx, myChoice HRD
  - Why
    - Not your typical CDx story, but a good CDx story, and maybe the best sort of CDx for Dx Company
    - Unique portfolio story
    - Topical: CDx, Regulatory, Pharma -Dx Partnerships
  - Stop me at anytime with General Questions on any related topic
- Discussion

# Myriad's Vision (but a moment on Myriad's Past)

***Answering Patient's Most Pressing Questions : 4 in 6 Strategy***




- Oncology
- Preventive Care
- Urology
- Autoimmune
- Dermatology
- Neuroscience

# Companion Diagnostic Partnerships

**Leader in Companion Diagnostics**

- Approximately 20 pharmaceutical partners

**Complete Biomarker Capability**

- DNA, RNA and Protein

**Major PARP Inhibitor Opportunity**

- Collaboration with 5 pharmaceutical companies

**Diverse Disease Indications**

- Cancer
- Depression
- Diabetes
- Autoimmune Disease

# Myriad's PARPi and Platinum CDx Program

**PARP Inhibitors:**

- Collaborations with five pharma partners
- Supporting 13 Phase 3 world-wide clinical trials
- Current indications include breast, ovarian and prostate cancer

**Platinum Drugs:**

- Guide treatment decisions for neoadjuvant, adjuvant and metastatic triple negative breast cancer
- All indications represent potential market of over one million patients

TESARO™

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

AstraZeneca

BIOMARIN®

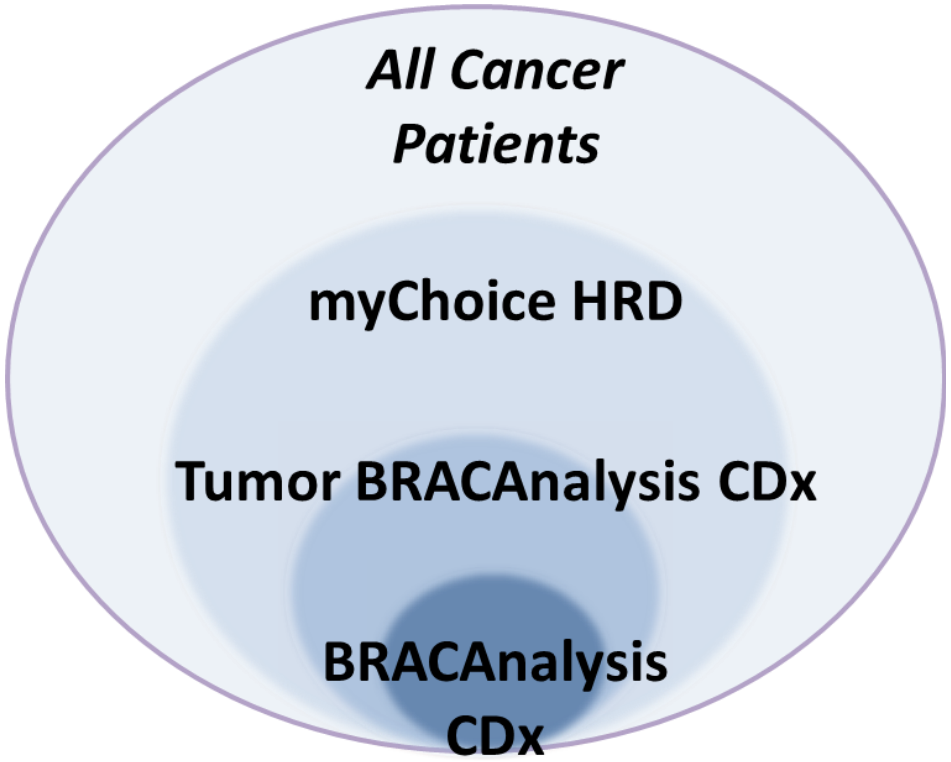
abbvie

# The Unique Evolution of "CLIA" BRACAnalysis

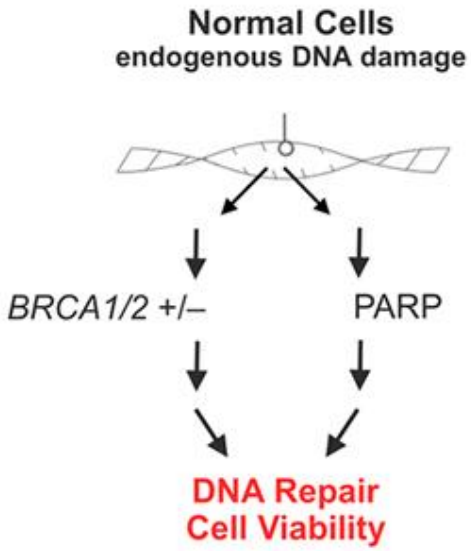
## *The History (simplified)*

- Clinical, CLIA-LDT Hereditary Cancer Testing for BRCA1 & BRCA2 mutations
- Farmer et al, Nature 2005
- Jan 2011, negative top-line results for iniparib disclosed by Sanofi
- Dec 2011- AZ halts development of olaparib in ovarian cancer
- 2013 Myriad – AZ enter into a CDx Co-development agreement
- Dec 19, 2014 FDA Approves Lynparza™ and BRACAnalysis CDx™

## *The Present*

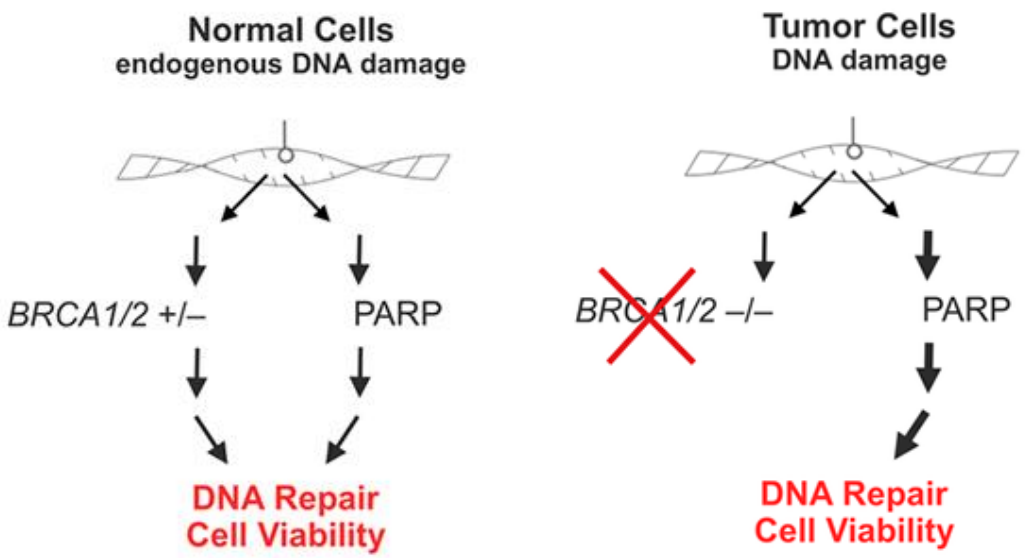


# Why are PARPi's Effective in *BRCA* Deficient Cells?




polyADP ribose polymerase (PARP) and *BRCA* both function to repair DNA

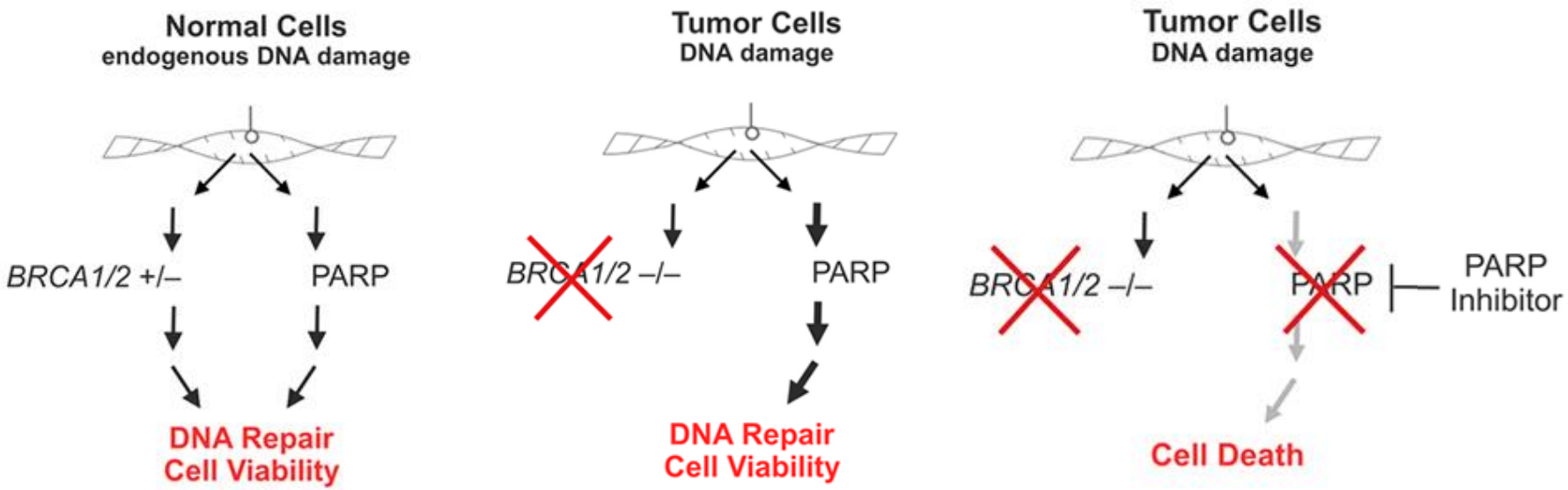
# Why are PARPi's Effective in *BRCA* Deficient Cells?




polyADP ribose polymerase (PARP) and *BRCA* both function to repair DNA

Tumors with *BRCA* mutations already have a DNA repair defect

# *BRCA* Mutations and PARPi's Cause Cell Death Due to Accumulation of DNA Damage



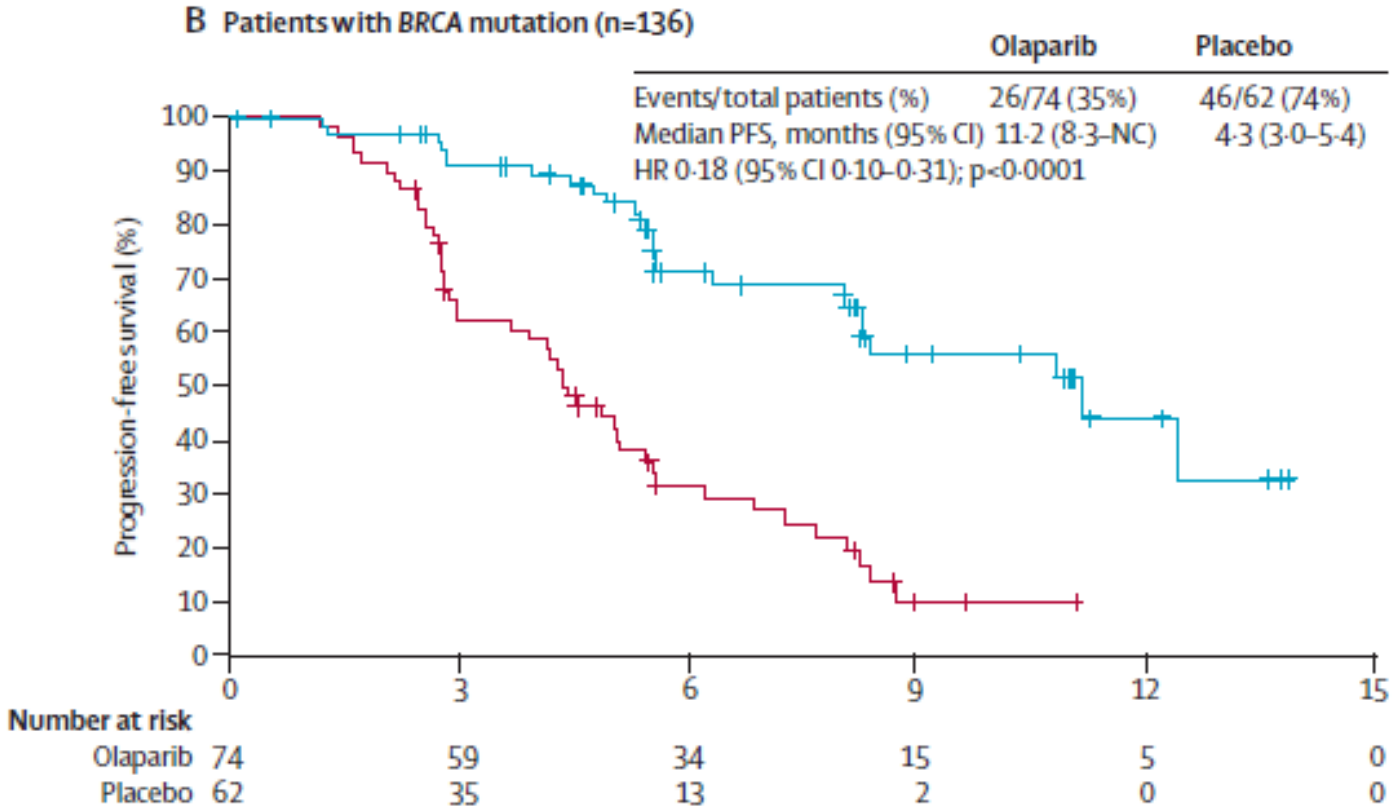

polyADP ribose polymerase (PARP) and *BRCA* both function to repair DNA

Tumors with *BRCA* mutations already have a DNA repair defect

Inhibiting PARP in *BRCA* deficient cells prevents the cell from replicating- effectively killing the cancer cells

# Patients with gBRCA Mutation Respond to Olaparib

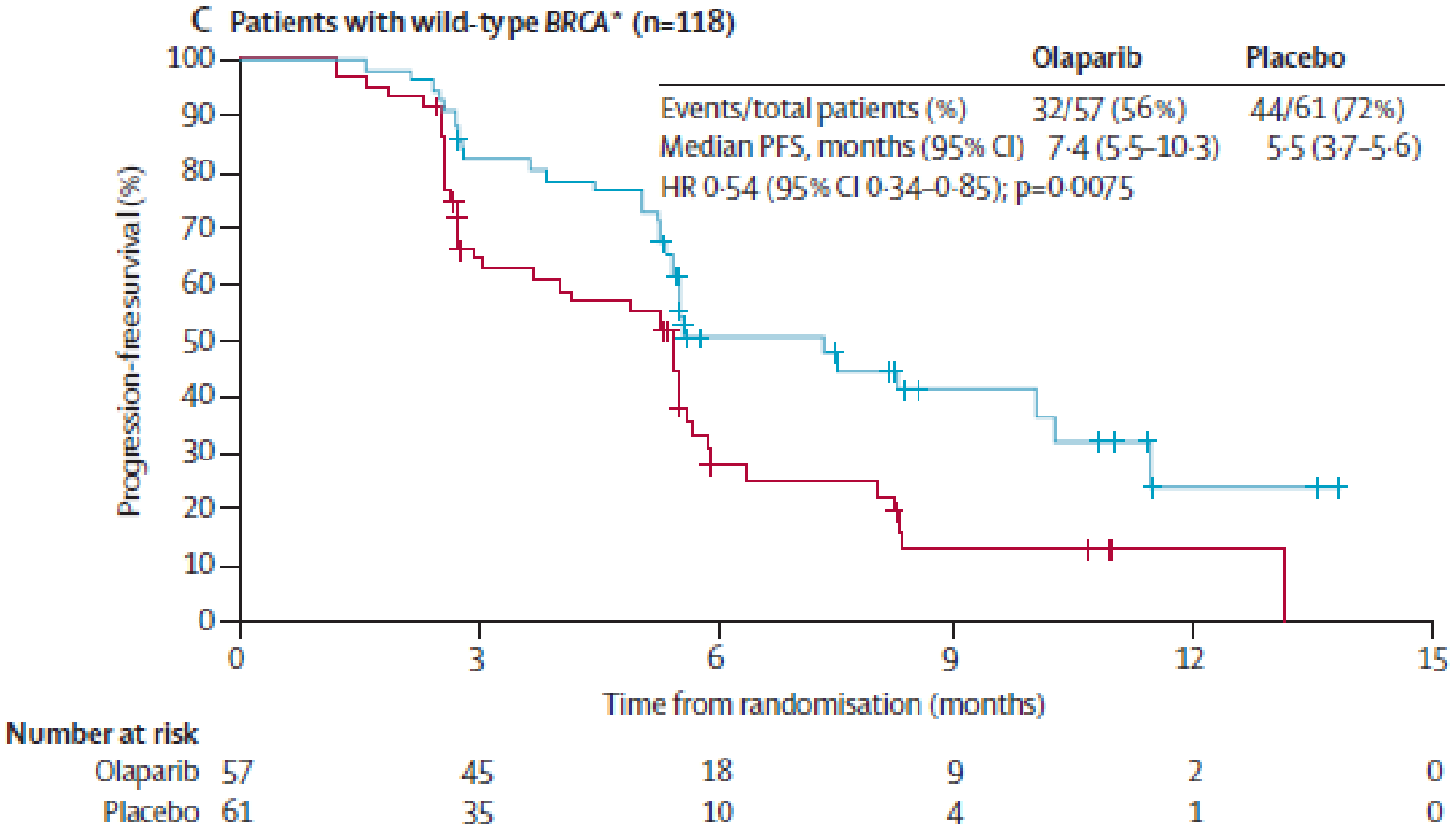
**Olaparib maintenance in Recurrent Platinum Sensitive Ovarian Cancer**




*ASCO 2013 & Lederman et al, Lancet Onc 2014*

# Subset of Patients w/o gBRCA Mutations Respond to Olaparib

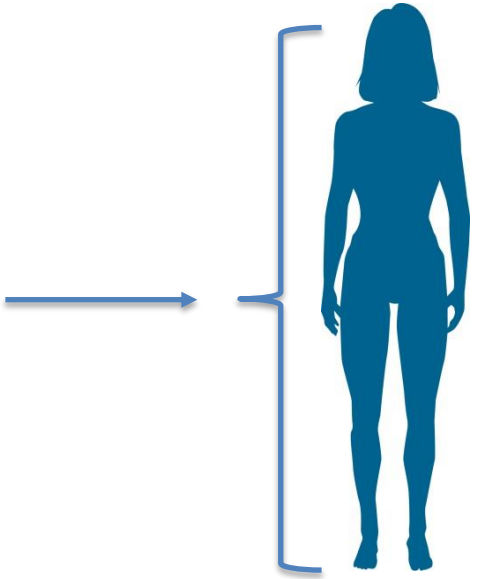
Can we identify those patients who are gBRCA1/2 *wt* and are responsive

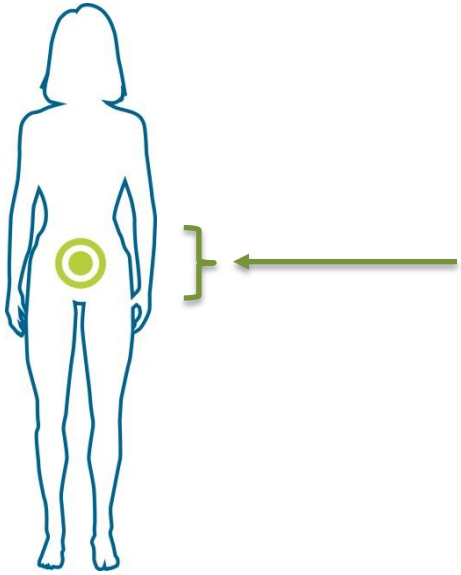



*ASCO 2013 & Lederman et al, Lancet Onc 2014*

# Somatic Mutations ID Some of the "Missing" Responders

- **Germline (hereditary) mutations** exist in the patient's germ cells and thus can be passed on to future generations





**Somatic (acquired) mutations** can spontaneously arise in any cell in the body (except germ cells) at any time during the patient's life

Tumor

# BRACAnalysis CDx™

## A companion diagnostic for Ovarian Cancer

*Guides the selection of patients for select PARP inhibitor therapy*

***Myriad Genetics, Inc.***

# Tumor BRACAnalysis CDx

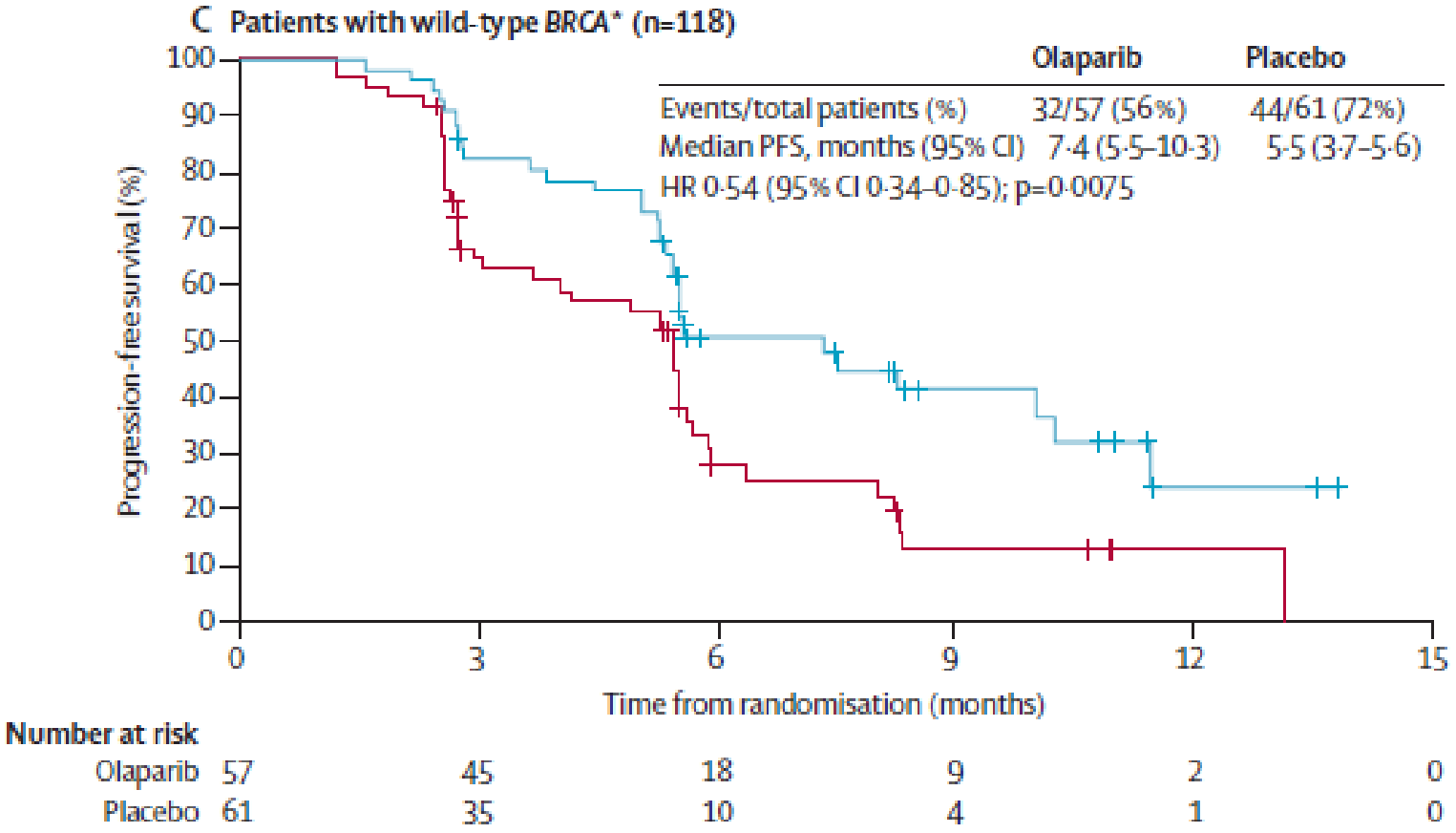
20 years of BRACAnalysis experience applied to testing FFPE tumor tissue

| **>99% test specificity and sensitivity** | **>97% variant classification for *BRCA1*/*BRCA2* mutations** |
|---|---|
| Ensuring accurate identification of those patients who could benefit from targeted treatment | Increasing certainty for patients and ensuring more patients have a clearer management pathway |
| **Average 14-day laboratory turnaround time** | **CE marking** |
| Timely reporting ensuring results are available to support clinical decisions | Verifying that Tumor BRACAnalysis, complies with all requirements of the European Directive for performance and safety |

Available as a CE marked product in Myriad Munich Laboratory

# Subset of Patients w/o gBRCA Mutations Respond to Olaparib

Can we identify those patients who are gBRCA1/2 *wt* and are responsive




*ASCO 2013 & Lederman et al, Lancet Onc 2014*

# Myriad's HRD Assay Development Approach

***Develop a DNA-based assay capable of detecting Homologous Recombination Deficiency (HRD) regardless of its etiology or mechanism***

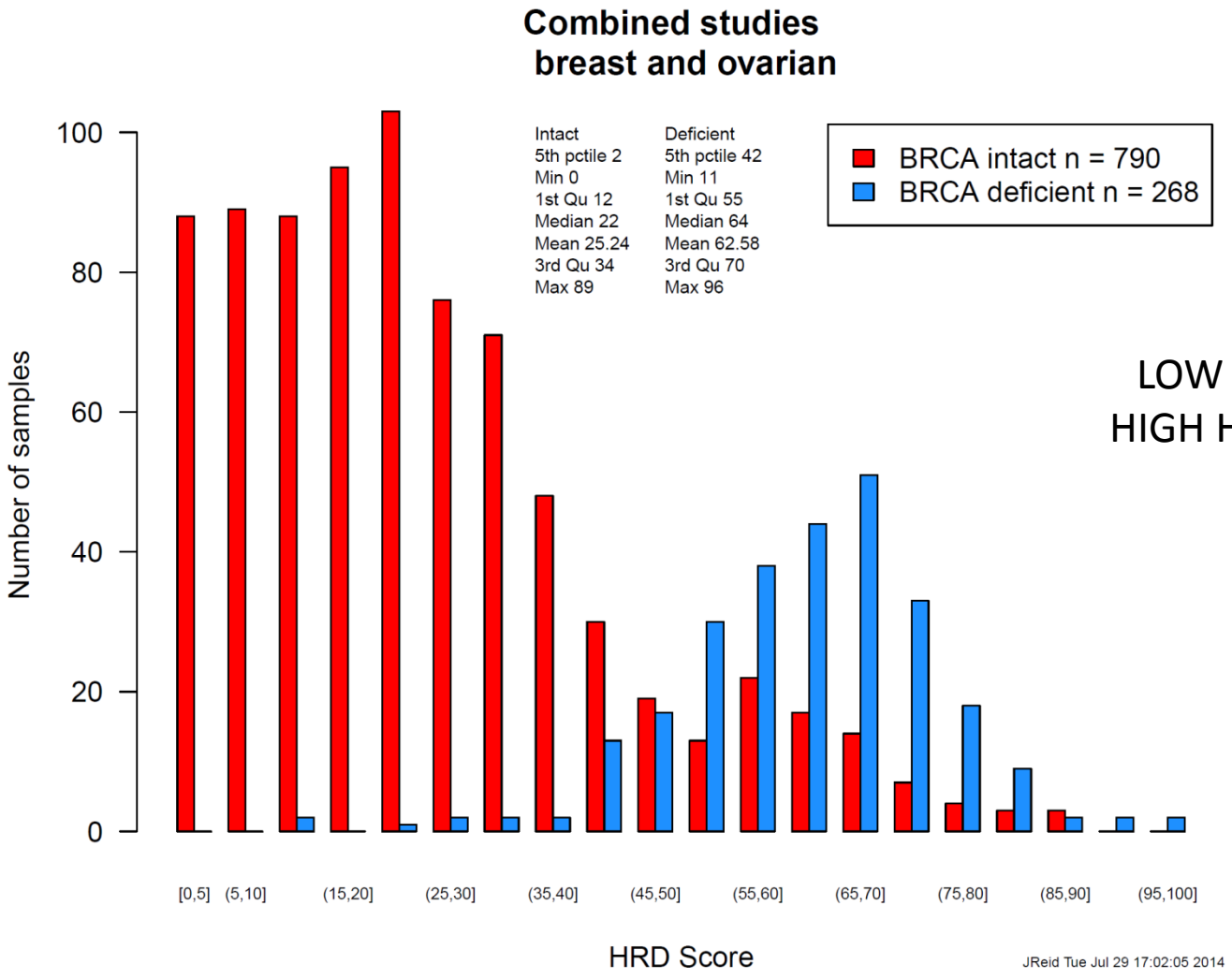
- No need to know all kinds of causal alterations in all relevant genes
- HR deficiency footprint should be the same in all cancer
- HR Deficiency status includes all known functional BRCA defects and captures "beyond BRCA" HR deficiencies

# Calculation of the HRD Score

- LOH Score: The number of LOH regions longer than 15 Mb but shorter than the length of a whole chromosome
- TAI Score: The number of regions with allelic imbalance which extend to the subtelomere but do not cross the centromere (Birkbak et al, Cancer Discovery 2012)
- LST Score: The number of chromosomal breaks between adjacent regions longer than 10 Mb after filtering out regions shorter than 3 Mb (Popova et al, Cancer Research 2012)

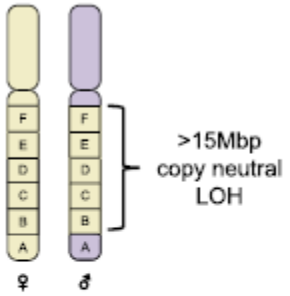
***"HRD Score " = TAI Score + LOH Score + LST Score***

# HRD Score Distribution

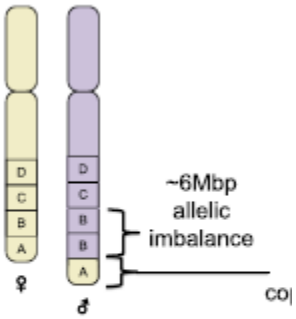



LOW HRD: 0 to 41
HIGH HRD: 42 to 100

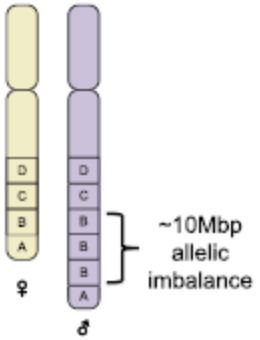
# myChoice HRD Rearrangements




| HRD | NtAi | LST |
|---|---|---|
| 1 | 0 | 1 |




| HRD | NtAi | LST |
|---|---|---|
| 0 | 1 | 0 |




| HRD | NtAi | LST |
|---|---|---|
| 0 | 0 | 1 |

**Figure 4:**

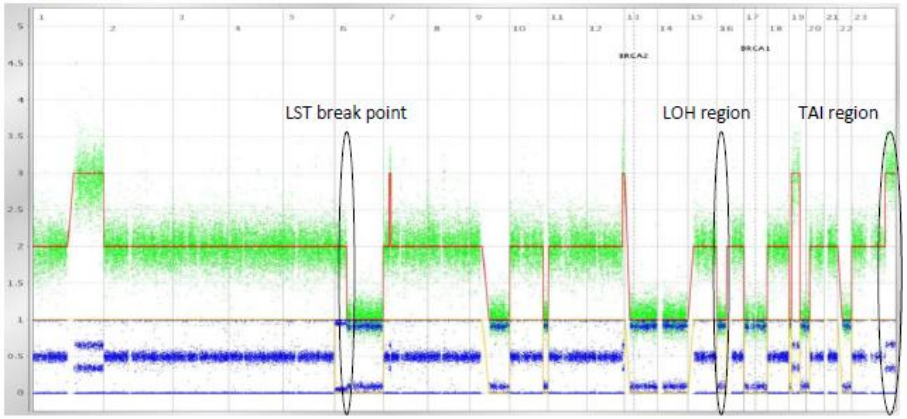
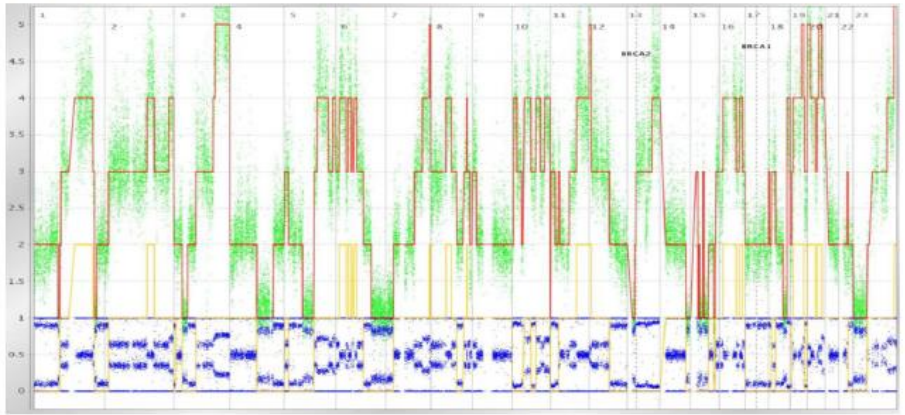
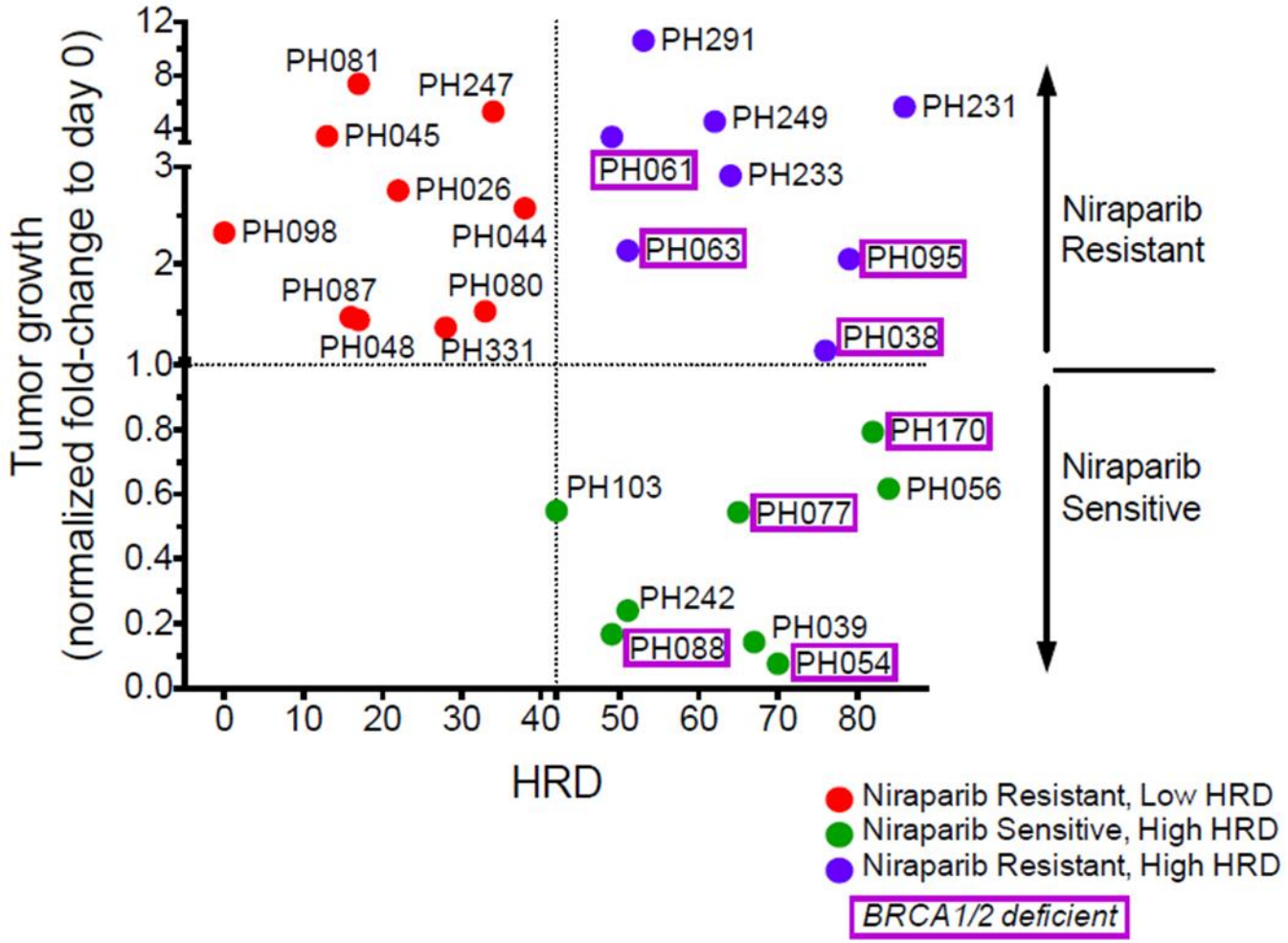



**Figure 5:**



# HRD applied to PDX models of TNBC and Ovarian Cancer




Wilcoxen et al. ASCO 2015

# myChoice HRD Predicts Response to Platinum Regimes

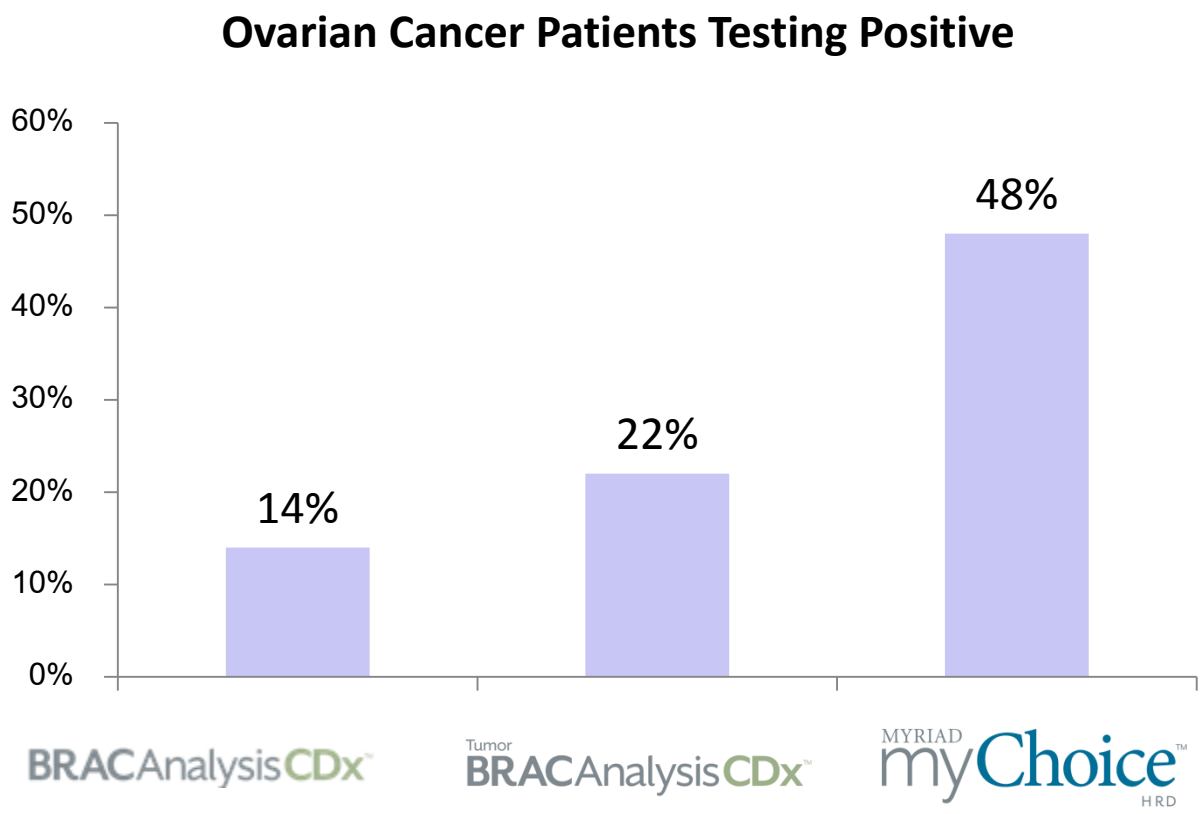
| TRIAL | Description | Overall Response | Response to platinum in HR deficient/non-def |
|---|---|---|---|
| PrECOG 0105 | Single arm<br>Gem/Carbo/Iniparib<br>93 patients | 36% | **41%/10%**<br>**RCB 0/1** |
| NCT01372579 | Single arm<br>Carbo/eribulin | 42% | **75%/14%**<br>**pCR** |
| NCT00148694<br>/NCT00580333 | Two Phase II studies<br>Cisplatin<br>Cisplatin+/-<br>bevacizumab | 15%<br>21% | **28%/0%**<br>**pCR** |
| Geparsixto | Randomized phase 2<br>Doxil/paclitaxel<br>/bevacizumab (PM) vs<br>PM + carbo | 53% | **64%/30% carboplat**<br>**34%/20% no carboplat**<br>pCR ypT0/ypN0 endpoint |

# 3 FDA-Approved CDx Tests: Complete Franchise

- BRACAnalysis CDx™: an in vitro diagnostic device intended […]to aid in identifying ovarian cancer patients […] eligible for treatment with Lynparza™ (olaparib).
- Tumor BRACAnalysis CDx™: an in vitro diagnostic […] using genomic deoxyribonucleic acid (DNA) extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. Results of the test may be used as an aid in treatment decision making for poly ADP ribose polymerase (PARP) inhibitors […].
- myChoice HRD™: TBD – but probably very similar

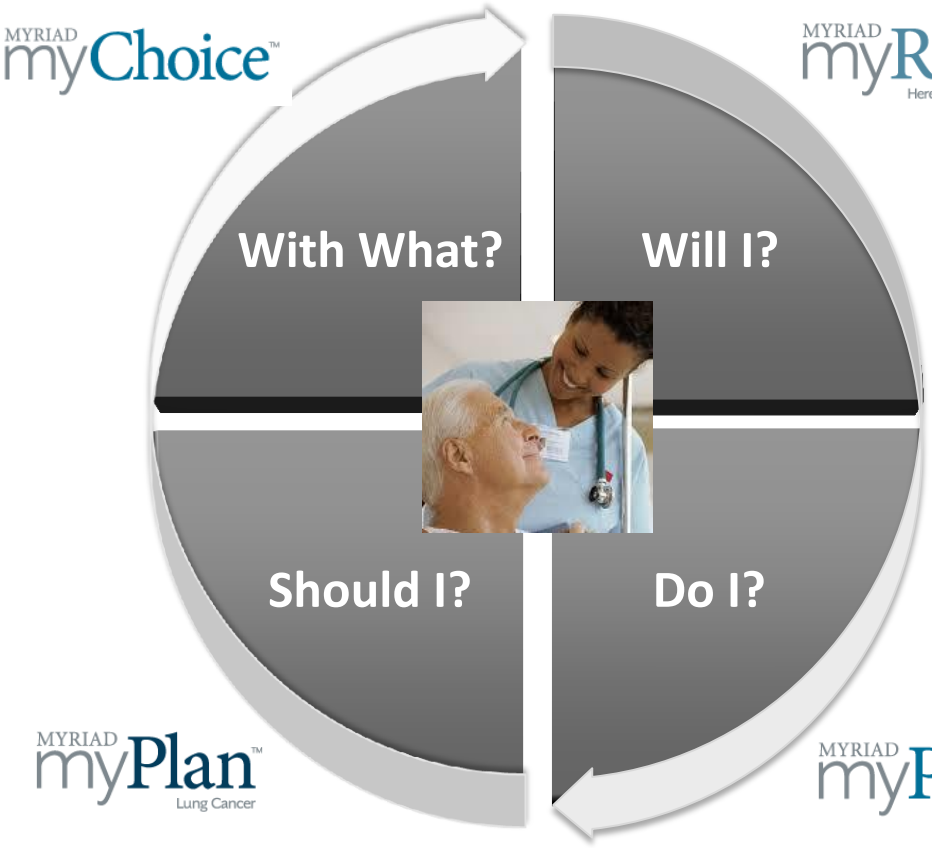
# Companion Diagnostic Portfolio

- Identify cancer patients with tumors that lack the ability to repair DNA
- Likely to respond to DNA damaging agents (PARP or platinum drugs)



# Myriad's Vision

***Answering Patient's Most Pressing Questions***




- Oncology
- Preventive Care
- Urology
- Autoimmune
- Dermatology
- Neuroscience